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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
LONNELLY, Y	
ART UNIT	**PAPER NUMBER**
1636	5

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/427,699	Ming Zhao
Examiner	**Group Art Unit**
Yvette Connell Albert	1633

Responsive to communication(s) filed on _____.

This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

X Claim(s) 1-11 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

X Claim(s) 1-11 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

X Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

X Notice of References Cited, PTO-892

X Information Disclosure Statement(s), PTO-1449, Paper No(s). 4

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

Notice of Informal Patent Application, PTO-152

--- *SEE OFFICE ACTION ON THE FOLLOWING PAGES* ---

DETAILED ACTION

Some references cited in the IDS have not been considered because they were not available with the ordered file, and as such, had to be ordered separately. As soon as these references become available, they will be considered.

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because : It does not state the PCT and the CIP numbers in the box provided.

Double Patenting

1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

2. Claims 1, and 3-7 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 8, 10, 13, 14, and 19 of U.S. Patent No. 5,753,263.

The claim language recited in the instant invention is drawn to a method to inhibit alopecia by delivering topically, an effective amount of a nucleotide sequence encoding the p21 protein to the hair follicles of a mammal. The claims are also broadly drawn to said nucleotide sequence contained within a vector or liposomal formulation, or wherein the vector is contained within a liposomal formulation.

Similarly, the claim language recited in the published patent is drawn to a method to introduce a composition containing at least one active ingredient which is effective to inhibit the loss of hair caused by a chemotherapeutic agent selectively to the hair follicles of a subject . . . . wherein the active ingredient is a protein which is a cell cycle inhibitor. . . . . wherein said composition comprises an expression system for the production of an effective amount of a protein which is a cell cycle inhibitor. The claims recited in the published patent are also drawn to cell cycle inhibitors selected from the group consisting of p16, p15, p21, p27, and p28; a liposomal formulation for delivery of a composition to hair follicles, wherein the active ingredient is a protein which is a cell cycle inhibitor; wherein the active ingredient is an expression system for production of an effective amount of a protein which is a cell cycle inhibitor, selected from the group consisting of p16, p15, p21, p27, and p28.

Although the conflicting claims are not identical, they are not patentably distinct from each other because they overlap in scope and both inventions provide for the inhibition of hair loss caused by a chemotherapeutic agent, by administering a cell cycle inhibitor, p21, or an expression system for the production of an effective amount of a protein which is a cell cycle inhibitor, p21, to hair follicle cells in a subject.

Therefore, claim language recited in the instant invention is an obvious variation of the claim language in the issued patent, which renders the scope of the conflicting claims in the instant invention, patentably indistinct.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1 and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is considered vague and indefinite because it is unclear how the delivery of a nucleotide sequence encoding p21 would inhibit alopecia.

Claim 8 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps involve the observation of p21 expression in hair follicle cells, via fluorescence, both *in vitro* and *in vivo*.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method to inhibit chemotherapy induced alopecia by the topical administration of an effective amount of a nucleotide sequence encoding the p21 protein, which upon expression would provide p21 to the hair follicle cells of a mammal, and the specification while being enabling for a method of observing the *in vitro* expression of p21 hair follicles in cells on a histoculture, by providing cells with an expression system contained in plasmid pEGFP-21, does not reasonably provide enablement for a method of inhibiting any and all alopecia, nor does the specification provide enablement for any *in vivo* method for observing the expression of p21 in hair follicle cells by providing cells with any expression system. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

1. Claimed invention. The claims are drawn to a method to inhibit alopecia by delivering topically, an effective amount of a nucleotide sequence encoding the p21 protein to the hair follicles of a mammal. The claims are also broadly drawn to said nucleotide sequence operably linked to control sequences, contained within a vector or liposomal formulation, or wherein the vector is contained within a liposomal formulation. The claims are further drawn to a method of observing the expression of p21 hair follicles in cells, wherein the expression system is contained in a plasmid, retroviral vector, or adenoviral vector, and wherein the cells are contained in a histoculture. Therefore, applicant is claiming a method whereby chemotherapy induced (CIA) or androgenic induced alopecia can be prevented or inhibited by the topical administration to the skin area of any mammal, a nucleotide sequence encoding p21 protein.

2. The results and examples of pages 8-9 shows that applicant was successful in cloning human p21 genes by amplifying the nucleotide sequence encoding the human p21 gene from plasmid MBP-p21 by PCR. The applicant was also successful in constructing the vector pEGFP-p21. Finally, applicant was successful in showing *in vitro*, via histoculture, that the EGFP-p21 gene was selectively expressed in hair follicles, as visualized by bright EGFP fluorescence.

3. It is not readily apparent given applicant's disclosure alone, that one skilled in the art would be able to practice the invention over the scope claimed in view of the lack of guidance provided in the specification as filed. In the instant situation, the claims embrace a method of inhibiting chemotherapy or androgen induced alopecia by the topical delivery of an effective

amount of a nucleotide sequence encoding the p21 protein to the skin areas of any mammal having a plurality of hair follicles. The specification gives specifics only for the p21 cyclin dependent kinase inhibitor(CDKI) and its role in inhibiting DNA synthesis, by preventing hair follicle cells from entering S-phase, thereby protecting cells against toxic events such as CIA. It remains unclear that the state of the art regarding CDKIs at the time of filing was such that one skilled in the art would have been able to routinely isolate and characterize any and all p21 CDKI from any mammalian species with the intended functionality of inhibiting or preventing all alopecia as broadly claimed, and further be able to inhibit any form of alopecia via expression of any p21. Such is considered to require undue experimentation.

The specification is not enabling in its disclosure as it fails to teach a specific vector containing an effective amount of a nucleotide sequence encoding the p21 protein. In addition, there is no correlation between vectors such that the vector utilized for inhibiting CIA alopecia would be suitable for inhibiting androgenic or other forms of alopecia. On page 5 of the specification, applicant in a preferred embodiment proffers the use of viral vectors such as adenoviral vectors, retroviral vectors or other mediators of cellular uptake such as lipids or liposomal formulations, for the integration of the p21 nucleotide sequence. However, the specification fails to teach how many vector particles, of which specific viral vector would be needed per target site, or whether or not this dosage of vector particles would fluctuate depending upon the regulatory or control sequences utilized, or whether or not increasing vector particle

production would be more or less labor intensive. Anderson states: "the retroviral vectors can only accommodate 6-8 kb of sequence and identifying all the components of a gene's regulatory system can be difficult, but emphasizes the need to develop vectors capable of gene transfer to specific cell types. He further states that the goal is to use regulatory sequences which respond to the body's own physiological signals, so that inserted therapeutic genes can function the way normal endogenous genes do". Anderson also teaches that retroviral vectors are biological agents which can only be made by living cells. Biological systems are not the easiest systems in which to carry out good manufacturing practice and quality assurance and control procedures(Anderson, see page 26, right col, 3rd para). In addition, retroviral vectors cannot be generated at a high titre, so that it is not possible to get a large number of vector particles to the desired cell type *in vivo*, as the viral particles would bind to many cells they encounter and be diluted out before reaching their target(Anderson, see page 25, right col, 2nd para). Therefore, in the absence of a specific viral vector taught for the administration of p21 to the hair follicles of a mammal, it would require undue experimentation to determine which viral vector, linked to which specific control sequence, would be most suitable for the delivery of p21 to hair follicle cells.

Similarly, the specification is not enabling in its disclosure as it fails to teach a specific lipid or lipid formulation to be utilized with the viral vector of the present invention. No teachings are present to guide the skilled artisan in the selection of a suitable lipid or lipid formulation or

composition, which when utilized would be efficacious in the delivery of the nucleotide sequence encoding the p21 protein, and in its concomitant expression in hair follicle cells.

The specification is not enabling in its disclosure as it fails to teach a specific control or regulatory sequence, linked to the nucleotide sequence encoding the p21 protein. On page 5 of the specification, applicant states that general constitutive promoters such as SV40 or CMV promoters can be included along with their enhancer elements, or tissue specific promoters may be used to enhance specificity, in controlling p21 gene expression in hair follicle cells. However, according to Anderson, "assuming that efficient gene transfer can be developed, the next issue is long-term stable gene expression at an appropriate level. Furthermore, the regulatory sequences that control gene expression often do not remain active. There is a tendency for the cell to recognize foreign promoters, particularly viral promoters such as SV40 and CMV and inactivate them by methylation or other mechanisms. If the gene stays active within the cell, the cell often dies, since the immune system is still likely to recognize a new or modified protein which will appear abnormal to an immune system that has never been exposed to it(Anderson, see page 26, right col)".

The specification is not enabling in its disclosure as it fails to teach the pharmaceutically acceptable composition or carrier of the topical agent to be applied to the skin areas of a mammal. No teachings are present to guide the skilled artisan in the selection of, by way of example, a solution, lotion, cream, gel or ointment which when administered topically, would be

therapeutically effective in inhibiting or preventing alopecia. Neither is guidance offered on how one skilled in the art would prepare the topical composition for administration, nor is guidance offered on whether or not the topical composition would be administered prophylactically or therapeutically, and if so, how often and at what dosage.

The specification is not enabling in its disclosure as it fails to teach a method whereby the *in vivo* expression of p21 in hair follicle cells would be observed. No guidance is provided to the skilled artisan in determining whether the p21 gene would be selectively expressed and sustained in hair follicle cells *in vivo*, neither is guidance offered in terms of how one would assess *in vivo*, efficient transduction in the absence of specific *in vivo* assays or tests to observe expression. Furthermore, the specification fails to teach the routes of administration, the frequency, and the dosage, such that p21 gene expression would be efficacious and observable, *in vivo*.

4. The physiological art of treating and preventing CIA induced alopecia, with epidermal growth factor (EGF) and Vitamin D3, appeared to render hair follicles resistant to the toxic effects of CIA, thus preventing hair loss, as demonstrated by Jimenez et al, US Patent No. 5,486,509. However, the physiological art of utilizing CDKI p21 to inhibit or prevent CIA alopecia in a mammal, at the time of filing, would have been considered unpredictable. At the time the invention was made, successful implementation of gene therapy protocols was not routinely obtainable by those skilled in the art via the expression of p21, in the treatment of CIA induced alopecia.

5. In the absence of specific guidance which is lacking in the specification as filed, and given the state of the art at the time of filing, coupled with the reasons discussed above, it would require undue experimentation for one skilled in the art to practice the methods or use the claimed products as disclosed in the specification.

The quantity of experimentation required to practice the invention as claimed would require an expression system contained in a viral vector and/or liposomal formulation, operably linked to control sequences, in a pharmaceutically acceptable composition, which when applied topically in a therapeutically effective dose, would inhibit or prevent alopecia in a mammal. This would require undue experimentation as one must first determine a nucleotide sequence encoding the p21 protein, obtained from any source, and/or chemically synthesized, and then determine which viral vector, linked to which promoter or control sequence, in the presence of which lipid formulation, in which pharmaceutically acceptable topical composition, and administered to a mammal, would be inhibit alopecia. This is considered trial and error experimentation in the absence of specific embodiments exemplified in the specification. The innumerable variables and permutations introduced in determining which given set of parameters which when combined would produce the intended functionality of inhibiting CIA or androgenic alopecia is considered undue.

Therefore, the specification while being enabling for a method to observe the *in vitro* expression of p21 in hair follicle cells, does not reasonably provide enablement for a method to

observe the *in vivo* expression of p21 in hair follicle cells, neither does it provide enablement for a method of inhibiting any and all alopecia, other than chemotherapy induced, by delivering a therapeutically effective amount of p21 hair follicles to the skin areas of any mammal.

Claim Rejections - 35 USC § 102

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.
>
> (f) he did not himself invent the subject matter sought to be patented.
>
> (g) before the applicant's invention thereof the invention was made in this country by another who had not abandoned, suppressed, or concealed it. In determining priority of invention there shall be considered not only the respective dates of conception and reduction to practice of the invention, but also the reasonable diligence of one who was first to conceive and last to reduce to practice, from a time prior to conception by the other.

7. Claims 1- 7 are rejected under 35 U.S.C. 102(e) as being anticipated by Lishko et al, US Patent No. 5,753,263.

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Applicant discloses a method to inhibit alopecia by delivering topically, an effective amount of a nucleotide sequence encoding the p21 protein to the hair follicles of a mammal. Applicant also discloses that said nucleotide sequence is contained within a vector or liposomal formulation, or wherein the vector is contained within a liposomal formulation.

Lishko et al teaches a method of preventing chemotherapy induced alopecia by delivering an expression vector comprising a nucleic acid molecule coding for p21, entrapped in a liposomal composition(col 45, lines 1-6).

Therefore, the claimed invention was clearly anticipated by Lishko et al.

Claims 1- 7 are directed to the same invention as that of claims 1-3, 8, 10, 13, 14, and 19 of commonly assigned US Patent No. 5,753,263. The issue of priority under 35 U.S.C. 102(g) and possibly 35 U.S.C. 102(f) of this single invention must be resolved.

Since the Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302), the assignee is required to state which entity is the prior inventor of the conflicting subject matter. A terminal disclaimer has no effect in this situation since the basis for refusing more than one patent is priority of invention under 35 U.S.C. 102(f) or (g) and not an extension of monopoly.

Failure to comply with this requirement will result in a holding of abandonment of this application.

Conclusion

No claims are allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yvette Connell, whose telephone number is 703-308-7942. The examiner can normally be reached on Monday-Friday from 8:00 to 4:30 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 703-308-0447.

Any inquiry of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

Yvette Connell

May 26, 2000

JOHN L. LeGUYADER
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